AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 13: Pulmonary Disease, Including Asthma

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U.S. Department of Health and Human Services
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www.ahrq.gov

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Prepared by:
ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Financial Disclosure Statement

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

Richard Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

Yen-pin Chiang, Ph.D.
Acting Director
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

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Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 150 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the two topics for which (1) preliminary phase III data on drugs, phase II or III data on devices and procedures were available, or programs were being piloted; (2) information was compiled before May 15, 2014, in this priority area; and (3) we received five to eight sets of comments from experts between July 1, 2013, and May 23, 2014. (Sixteen topics in this priority area were being tracked in the system as of May 15, 2014.) We present summaries on two topics (indicated below by an asterisk) that emerged as having high-impact potential on the basis of experts' comments, both of which were in the December 2013 Potential High-Impact Interventions report. A third topic that was in the December 2013 report, the oral tablet ivacaftor (Kalydeco™, Vertex Pharmaceuticals, Inc., Cambridge, MA) for treatment of cystic fibrosis in patients with G551D-CFTR mutation, was removed from this iteration of the high impact report. This drug was approved for marketing in January 2012 and is now classified as diffused according to the Horizon Scanning protocol and has thus, been archived. The material in this Executive Summary and report is organized alphabetically by intervention. Readers are encouraged to read the detailed information on these interventions that follows the Executive Summary.

Priority Area 13: Pulmonary Disease, Including Asthma

Topic	High-Impact Potential
1. * Off-label azithromycin for prevention of chronic obstructive pulmonary disease exacerbations	Lower end of the high-impact-potential range
2. * Portable warm blood perfusion system (Organ Care System) for lung transplantation	High

Discussion

Pulmonary disease is a priority area in which relatively few interventions have been identified as meeting criteria for tracking in the AHRQ Healthcare Horizon Scanning System, despite extensive scanning. Experts deemed two topics as having high-impact potential: an off-label use of the antibiotic azithromycin to prevent chronic obstructive pulmonary disease (COPD) exacerbations; and a novel, portable, warm-blood perfusion system for lung transplantation.

Off-Label Azithromycin for Prevention of Chronic Obstructive Pulmonary Disease Exacerbations

- **Key Facts:** COPD is the third most common cause of death and chronic complications in the United States. Acute COPD exacerbations dramatically change the disease course and are associated with a rapid decline in patients' lung function and worsening quality of life. Better treatments to prevent COPD exacerbations are needed. Although antibiotic therapy is often given during an exacerbation, published clinical guidelines have recommended it not be used ongoing to prevent future exacerbations. However, a recent study on azithromycin use to prevent exacerbations has garnered new interest in prophylactic COPD therapy. Results of a randomized controlled trial (RCT) on prophylactic azithromycin for COPD exacerbations were published in 2011 in the *New England Journal of Medicine*. Azithromycin (Zithromax®, Pfizer, Inc., New York, NY), is a macrolide antibiotic with broad-spectrum activity that binds to the 50S ribosomal subunit of susceptible bacteria, interfering with microbial protein synthesis. Macrolide antibiotics also purportedly have anti-inflammatory properties, which could play a role in preventing COPD exacerbations. Azithromycin is being evaluated for off-label use to prevent COPD exacerbations and slow disease progression in patients who continue to have acute exacerbations despite receiving standard care. The drug has been administered orally, at a dosage of 250 mg once daily or three times weekly for this purpose. In May 2002, the U.S. Food and Drug Administration (FDA) approved azithromycin for treating acute bacterial COPD exacerbations due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae* infection. Azithromycin is not approved for prophylaxis of COPD exacerbations in patients at elevated risk but could be used off label in this patient population.

  In the RCT, patients with COPD (n=1,142) at increased risk of exacerbations received azithromycin 250 mg daily or placebo for 1 year in addition to standard care to determine whether daily azithromycin could reduce the frequency of COPD exacerbations. Patients treated with the drug were reported to have a longer median time to the first exacerbation (266 days vs. 174 days) and less-frequent exacerbations than patients treated with placebo. A post-hoc analysis of this study also demonstrated prophylactic azithromycin could increase the time to next hospitalization. In a later study, azithromycin three times weekly was shown to improve cough-specific health status compared with placebo. Adverse events associated with azithromycin included hearing loss and cardiac arrhythmias and concerns about antibiotic-resistance with daily use.

  Based on a March 2014 query of U.S.-based, online aggregator of prescription drug prices, a 1-month supply of azithromycin (generic) costs about $44, so the drug would be relatively inexpensive for long-term, prophylactic use.
- **Key Expert Comments:** Overall, experts commenting on this intervention stated that daily prophylactic azithromycin has the potential to reduce the rate of exacerbations in patients with COPD. Slowed disease progression could lead to improved quality of life and reduced costs. Azithromycin is not expected to replace treatment but to be additive to COPD treatment options. Experts commenting on this topic thought azithromycin would minimally disrupt patient management while potentially reducing the incidence of serious complications. They did, however, express concern about antibiotic resistance with ongoing daily use and whether other macrolides would be better suited for prophylactic use.
- **Potential for High Impact:** Lower end of potential high-impact range

Portable Warm Blood Perfusion System (Organ Care System) for Lung Transplantation

- **Key Facts:** Only about 10% to 30% of donated lungs are considered to be suitable for transplantation, according to lung transplant and organ donor experts. In 10% to 20% of patients who have undergone lung transplantation, donor lungs have been so severely damaged by the time of transplantation that the patient requires additional supportive therapies (i.e., ventilation, pharmacologic interventions). Developing new strategies to better preserve or improve donor-lung quality could affect the number of lungs available for transplantation. Standard methods of donor organ preservation expose the organ to sustained periods of ischemia and hypothermia, which can result in organ damage that can make an organ unsuitable for transplantation. The Organ Care System for lung preservation (OCS Lung) is in development by TransMedics, Inc. (Andover, MA). The OCS Lung is a portable, ex-vivo, warm blood perfusion, ventilation, and monitoring system that purportedly maintains the donor lungs in a "near physiologic state," potentially optimizing organ health and allowing for continuous evaluation during transport. The company calls it a "living organ" transplant. The OCS Lung consists of a portable, battery-operated console with a wireless monitor, a perfusion module described by the manufacturer as a "transparent, sterile chamber designed to protect the organ and maintain the appropriate, warm temperature and humidity," and a solution set to deliver nutrients to the preserved donor lungs. In pilot trials, the OCS Lung console was connected to the donor lung via the pulmonary artery and the trachea. Blood is delivered through the pulmonary artery and drains directly into the perfusion module chamber. A ventilator delivers air to the lungs via the trachea. Donor lungs are perfused with a solution enriched with two red blood cell concentrates that are matched to the intended transplant recipient. With the OCS, clinicians can measure the oxygen concentration in the blood to assess lung function. OCS Lung may also improve donor lung condition so that lungs previously considered as marginal in quality are transplantable. This would increase the number of viable organs for transplantation. Furthermore, by replacing static hypothermic storage with active perfusion, the technology is said to reduce organ-damaging cold ischemic time (particularly during transport from donor to recipient). This potentially increases the time an organ can be maintained outside the body before transplantation. The OCS has also completed trials for preserving donor hearts.

  In April 2014, the manufacturer filed with FDA for 510(k) premarket notification clearance to market the OCS Heart platform. If cleared for marketing, it would be the first portable, warm-blood perfusion system to reach the U.S. market. Its cost for the U.S. market is unknown. If cleared, use of the system would be part of the bundled payment for organ harvesting and transplantation. The system is available in Europe, and one report indicated that hospitals there pay about $60,000 for each machine.
- **Key Expert Comments:** A high unmet need exists to increase the number and quality of transplantable donor lungs, the experts commented. The OCS system has a high potential to increase the pool of viable lungs and increase the quality of transplanted lungs, the experts generally agreed. They expressed enthusiasm about provider and patient acceptance of this technology. Additionally, the OCS Lung could reduce transplant-associated complications and adverse events. Some experts thought the OCS Lung could alleviate the intensity and complexity of overall treatment after transplantation. In evaluating health disparities, some experts thought the OCS Lung would not have an effect; however, others suggested the high

costs of acquiring the OCS Lung equipment and limited access to health care coverage for organ transplantation by health disparate groups could further contribute to health disparities.

- **Potential for High Impact:** High

Pulmonary Disease, Including Asthma, Interventions

Off-Label Azithromycin for Prevention of Chronic Obstructive Pulmonary Disease Exacerbations

Unmet need: Chronic obstructive pulmonary disease (COPD) is the third most common cause of death and chronic complications in the United States.[1] Acute COPD exacerbations dramatically change the disease course and are associated with a rapid decline in lung function and worsening quality of life. Better treatments to prevent COPD exacerbations are needed.[2]

Intervention: Azithromycin (Zithromax®), a broad-spectrum antibiotic in the azalide subclass of macrolide antibiotics.[3] Azithromycin binds to the 50S ribosomal subunit of susceptible bacteria, interfering with microbial protein synthesis.[3] Additionally, macrolide antibiotics purportedly have anti-inflammatory properties (reducing expression of cytokines, chemokines, leukotriene B_4 and matrix metalloproteinases),[4] which are thought to play a role in preventing COPD exacerbations and could position the drug as a useful adjunct to standard care.[5] Macrolide antibiotics also purportedly decrease expression of adhesion molecules that promote neutrophil accumulation in the lungs—neutrophils are a principal mediator of inflammation and tissue destruction.[4] Lastly, azithromycin is thought to improve airway clearance of apoptotic cells and bacteria, reducing secondary necrosis that occurs from release of cellular toxins that could contribute to inflammation.[6]

Azithromycin is being evaluated off label to prevent COPD exacerbations and slow disease progression. In trials, the drug has been given orally, 250 mg, once daily or three times weekly.[2,7] According to a published report, prophylactic azithromycin would be used in patients who continue to have acute exacerbations despite receiving standard care. Another patient-selection criterion for the treatment is having had at least two acute exacerbations the previous year as a baseline to assess treatment response and to limit overuse of azithromycin.[5]

Clinical trial: In a randomized controlled trial (RCT), patients with COPD who were at increased risk of exacerbations received azithromycin 250 mg daily (n=570) or placebo (n=572) for 1 year plus standard care to determine whether daily azithromycin reduced COPD exacerbations. The median time to first exacerbation was 266 days (95% confidence interval [CI], 227 to 313) among patients treated with azithromycin and 174 days (95% CI, 143 to 215) among patients receiving placebo ($p<0.001$). The frequency of exacerbations was 1.48 exacerbations per patient-year in the azithromycin group and 1.83 per patient-year in the placebo group ($p=0.01$). The hazard ratio (HR) for having an acute COPD exacerbation was 0.73 per patient-year (95% CI, 0.63 to 0.84) in the azithromycin group ($p<0.001$). Hearing decrements were more common in the azithromycin group than in the placebo group (25% vs. 20%, $p=0.04$).[2]

In a post-hoc analysis, described in Albert et al., patients who were hospitalized for a respiratory event during the study were tracked to determine the time to next hospitalization. Patients treated with azithromycin experienced 156 respiratory-related hospitalizations compared with 200 in patients given placebo (HR 0.82; 95% CI, 0.64 to 1.07). Azithromycin significantly increased the time between the first respiratory-related hospitalization and the second hospitalization compared with placebo (HR 0.58, 95% CI, 0.34 to 0.99); this effect started to occur about 40 days after discharge.[8]

In another RCT, the effects of prophylactic azithromycin on cough-specific health status (measured with the Leicester Cough Questionnaire [LCQ]) in patients (n=84) with COPD and chronic productive cough were assessed. Patients treated with azithromycin three times weekly showed clinically significant improvement in LCQ total score at 12 weeks compared with placebo (difference 1.3 ± 0.5: 95% CI, 0.3 to 2.3, $p=0.01$).[7]

Adverse events associated with azithromycin use include angioedema and cholestatic jaundice, which are potentially serious but were reported rarely. In clinical trials, adverse events that were most associated with patients discontinuing treatment were nausea, vomiting, diarrhea, and

abdominal pain.[3] Other adverse events associated with azithromycin that could dissuade a physician from prescribing it for prophylaxis in COPD patients include hearing loss and cardiac arrhythmias.[2,3,9] Additionally, investigators note concerns about developing antibiotic-resistant bacteria in patients treated with daily azithromycin.[2,10]

Manufacturer and regulatory status: Pfizer, Inc., of New York, NY, makes azithromycin. In May 2002, the U.S. Food and Drug Administration (FDA) granted marketing approval for azithromycin for treating acute bacterial COPD exacerbations due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae* infection.[11] FDA has not approved azithromycin for prophylaxis of COPD exacerbations in patients at elevated risk; some researchers have explored use of the drug in this patient population, an off-label use.

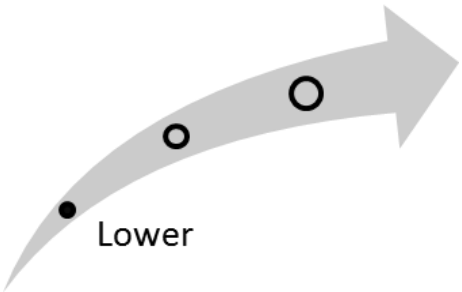
Diffusion: Ongoing prophylactic antibiotic use to reduce COPD exacerbations does not appear to have diffused widely because clinical guidelines have recommended against it, but those guidelines refer to evidence that predated the 2011 publication of new data from the RCT described above.[2]

Based on a March 2014 query of U.S.-based, online aggregator of prescription drug prices, a 1-month supply of azithromycin (generic) costs about $44, so the drug would be relatively inexpensive for long-term, prophylactic use.[12]

Clinical Pathway at Point of This Intervention

COPD treatment focuses on managing stable disease and exacerbations. Treatment includes smoking-cessation counseling and nicotine-addiction treatment, medications to address airflow limitations and inflammatory responses (i.e., long-acting bronchodilators, inhaled glucocorticosteroids), and antibiotics for lung infections. Clinicians also recommend that patients with COPD receive annual flu vaccinations and a pneumococcal polysaccharide vaccination. None of these approaches halts disease progression. In cases of advanced disease, supplemental oxygen or surgery (i.e., lung volume reduction, lung transplantation) may be recommended.[13] Azithromycin has been proposed as prophylactic, ongoing therapy to reduce the frequency of disease exacerbations, which may slow disease progression.

Figure 1. Overall high-impact potential: off-label azithromycin for prevention of chronic obstructive pulmonary disease exacerbations



Overall, experts commenting on this intervention stated that daily prophylactic azithromycin has potential to reduce the rate of exacerbations in patients with COPD. Slowed disease progression could lead to improved patient quality of life and reduced costs. To reduce costs and risks while gaining the benefits of prophylactic azithromycin use, one clinical expert stated, the ideal dosing for azithromycin could be three times weekly. Some experts expressed concern about antibiotic resistance and whether other macrolide antibiotics would be better suited for prophylactic use. Prophylactic azithromycin, if used, would be added to standard COPD treatment and would not

disrupt daily patient management. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, or health systems backgrounds, offered perspectives on this intervention.[14-20] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: No cure exists for COPD, the third leading cause of death and a significant source of health care costs, the experts stated. COPD exacerbations can lead to significant declines in lung function and progression towards respiratory failure. Prophylactic use of azithromycin or other macrolide antibiotics seem to be a promising treatment to slow COPD progression, particularly in patients with moderate to severe COPD, the experts stated. However, side effects including hearing loss, potential arrhythmias, drug resistance, and gastrointestinal issues must be monitored during prophylactic azithromycin use, the experts warned.

Acceptance and adoption: Clinicians might readily accept azithromycin as a simple, noninvasive, and affordable treatment to prevent exacerbations and slow COPD progression, with some caveats, noted the experts. These caveats—risks of hearing loss, cardiac arrhythmias, and antibiotic resistance—are factors that would make some physicians reluctant to prescribe the antibiotic, some experts stated. However, azithromycin is a widely used drug that clinicians are generally comfortable prescribing for treating infections, the experts noted. The experts also stated patients would likely generally accept a simple, relatively low-cost treatment that could prevent their quality of life from declining. Potential barriers to patient acceptance and adherence could include gastrointestinal disturbances and that azithromycin could take up to 6 months for patients to fully benefit from treatment, some experts noted.

Health care delivery infrastructure and patient management: If azithromycin is effective in preventing COPD exacerbations, reductions in pulmonary, acute, long-term, and intensive care units could be realized, the experts theorized. Although the cost of azithromycin therapy would be added to standard treatment costs, its low cost and its potential to offset costs of complications were seen by some experts as having a neutral or perhaps even cost-saving impact (especially when dosed 3 times per day). Prophylactic azithromycin use could increase the need for physician visits to monitor cardiovascular and hearing side effects, the experts noted.

Health disparities: Clinical experts stated that prophylactic azithromycin use could reduce health disparities by reducing the need for patients to require access to the health care system. Additionally, availability of generic versions of the drug and the practice of dosing three times weekly could reduce the cost of the drug for patients who struggle with the cost of drug co-payments. Overall, clinical experts thought the treatment's benefits outweigh the costs.

Portable Warm Blood Perfusion System (Organ Care System) for Lung Transplantation

Unmet need: In 2012, 28,051 people received organ transplants (about 79 per day); however, because of a shortage of donated organs, an average of 18 people die each day while waiting for a donor organ.[21] The process of organ transplantation from donor to recipient can alter organ homeostasis and affect both the speed at which and degree to which normal organ function returns.[22] Standard methods of organ preservation expose the organ to sustained periods of ischemia and hypothermia, which can damage donor organs.[22,23] Only about 10% to 30% of donated lungs are considered to be suitable for transplantation,[23] and in 10% to 20% of patients who have undergone lung transplantation, donor lungs have been so severely damaged by the time of transplantation that the patient requires additional supportive therapies (i.e., ventilation, pharmacologic interventions).[24] Developing new strategies to better preserve or improve donor-lung quality could affect the number of lungs available for transplantation.[23]

Intervention: The Organ Care System (OCS) Lung is an integrated and portable ex-vivo lung perfusion system intended to assess and improve marginal lungs and potentially to preserve or improve the condition of routine donor lungs. The system's potential advantages over conventional organ preservation methods include immediate and sustained donor lung recruitment at the donor site; reduced time for the organ to be maintained in a cold ischemic state, especially during transport; and continuous organ-quality assessment during transport from donor to recipient.[25] Furthermore, the system can potentially increase the time an organ is maintained outside the body in good condition before transplantation.[26] The company calls this a "living organ" transplant.

The OCS Lung preservation system consists of a portable, battery-operated console with a wireless monitor, a perfusion module described by the manufacturer as a "transparent, sterile chamber designed to protect the organ and maintain the appropriate, warm temperature and humidity," and solution set to deliver nutrients to the preserved donor lungs. The central platform component is the perfusion module chamber that protects and maintains the lungs. The platform also includes an oxygen supply, ventilator, and a blood pump. The monitor controls the platform and provides information that enables assessment of the donor organ.[26,27]

In pilot trials, the harvested lung was connected to the OCS Lung by means of the pulmonary artery and trachea. Blood is delivered through the pulmonary artery and drains directly into the perfusion module chamber. A ventilator delivers air to the lungs via the trachea. Donor lungs are perfused with a solution (Steen solution, Vitrolife AB, Göteborg, Sweden) that is enriched with two red blood cell concentrates, matched to the transplant recipient. The enriched solution is also supplemented with other compounds, including cefazolin, ciprofloxacin, voriconazole, methylprednisolone, glucose, multivitamins, and THAM buffer.[26]

While donor lungs are undergoing warm perfusion and ventilation in the OCS system, clinicians can assess the donor lung's functional capacity by measuring the oxygen concentration in the blood. Once on site for transplantation, warm blood perfusion is stopped, and the lungs are cooled using a heat exchanger or cold flush perfusion. After the lungs are immersed in cold low-potassium solution, transplantation may begin.[26]

Clinical trials: Two trials of the OCS Lung have been completed, and one phase III trial is ongoing and has reported preliminary data. One trial investigated the OCS Lung's feasibility for lung preservation during lung transplantation.[26] Warnecke and co-authors reported that "all grafts and patients (n=12) survived to 30 days; all recipients recovered and were discharged from hospital." A second trial investigates tissue alteration in donor lungs preserved with the OCS Lung compared with standard care.[28] As reported by Calabrese et al., "no significant morphological difference were observed in terms of: intraalveolar edema, capillary congestion, and intraalveolar

hemorrhage. OCS lung donors showed less leucocyte margination and significant less apoptosis both at cold ischemia time and after reperfusion."[28] Preliminary results from the phase III, INSPIRE trial have been reported in a press release from the manufacturer, stating: "The donor lungs preserved using the OCS Lung technology had significantly lower incident of severe primary graft dysfunction grade 3 (PGD3) after lung transplantation as compared to lungs that were preserved using cold storage. In addition, other important clinical parameters like in-hospital mortality, six months survival, rate of lung related complications, time on mechanical ventilation and ICU [intensive care unit] time were better in the OCS group as compared to cold storage."[29] Another ongoing phase III trial, International Trial to Evaluate the Safety and Effectiveness of The Portable Organ Care System (OCS™) Lung For Recruiting, Preserving and Assessing Expanded Criteria Donor Lungs for Transplantation (EXPAND Trial) (NCT01963780), will also measure patient survival and PGD3.[30]

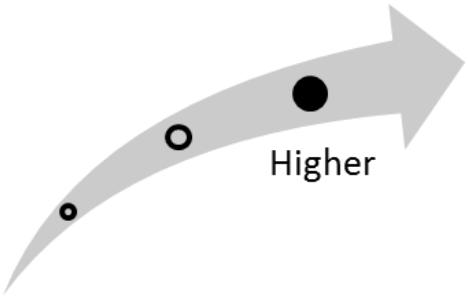
Manufacturer and regulatory status: The OCS Lung is being developed by TransMedics, Inc. (Andover, MA), for donor organ preservation during lung transplantation.[31] The OCS was also evaluated in clinical trials for donor heart preservation. In April 2014, the manufacturer reported pivotal trial data for the OCS Heart platform, which was part of its 510(k) premarket notification filing to obtain marketing clearance.[32] In January 2011, the OCS Lung received a Conformité Européene (CE) mark and is in use in Europe.[26] If cleared for marketing by FDA, the OCS Lung would be the only portable, warm-blood perfusion system available in the United States for donor lung preservation.

Diffusion: The system is in the innovation phase in the United States. If cleared for marketing, reimbursement for use of the system would be part of the bundled payment for organ harvesting and transplantation. The manufacturer has not provided any information about the cost of the OCS Lung. One report (CNN, April 2013) indicated that hospitals in Europe pay about $60,000 for each machine.[33]

Clinical Pathway at Point of This Intervention

The standard method for preserving donor lungs for transplantation is cold flush and static cold storage. This method has traditionally been successful for high-quality donor organs when the ischemia times are not excessive.[26] At the onset of the cold-storage process, the lungs are flushed with a cold solution in an anterograde and retrograde manner to clear the blood from the organ and to ensure proper reperfusion upon transplantation.[24,34] After flushing, the lungs are cooled and stored between 4 and 8 °C to reduce the metabolic rate and slow the degeneration process.[24] Inflated donor lungs are considered to be optimal; collapsed lungs do not tolerate ischemia very well. Lung inflation is done with an inspired oxygen tension of 30% to 50%.[34] The donor lungs are immersed in additional cold preservation solution and placed on ice for transport.[24] The total ischemic time is generally less than 8 hours.[34] The OCS Lung system would replace this method if approved for marketing and adopted.[35]

Figure 2. Overall high-impact potential: portable warm blood perfusion system (Organ Care System) for lung transplantation



Experts commented that the unmet need is great for more and higher-quality, transplantable donor lungs and generally agreed that this intervention has high potential to increase the pool and quality of viable donor lungs. Experts were optimistic about both provider and patient acceptance of this technology. The OCS Lung could reduce transplantation-associated complications and adverse events, the experts noted. Some experts anticipated the OCS Lung could alleviate the intensity and complexity of overall treatment after transplantation. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, or health systems backgrounds, offered perspectives on this intervention.[36-42] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A substantial unmet need exists for more and higher-quality, transplantable donor lungs; OCS could address that need, most experts agreed. However one expert expressed the caveat that the demand for donor lungs is much lower than the demand for kidneys and livers. Patient health outcomes could be improved by the purported increase in lung tissue quality from the OCS process, experts noted. However, they called for more safety and efficacy data, as well as long-term efficacy data, to support this claim.

Acceptance and adoption: Clinician acceptance and adoption of the system is expected to be high, according to the experts. Two experts, one with a health devices perspective and one with a clinical perspective, anticipated that adoption of the OCS Lung would be contingent on a cost-benefit analysis showing that the system improves outcomes over the standard methods of donor organ preservation.[36,39]

Health care delivery infrastructure and patient management: Transplantation-associated complications and adverse events could be reduced by the OCS Lung, the majority of experts suggested. Patient length of stay and staff needed for treating transplant complications could be significantly reduced with widespread use of the OCS Lung if it truly improves lung quality, the experts theorized. Some experts remarked on a possible learning curve for widespread use of the OCS Lung, highlighting the training required to properly operate the system. In terms of patient management, the potential for increased availability of lungs for transplantation could cause a small disruption. Furthermore, the potential exists for altering the standard practices for lung transplantation, in both harvesting and implanting donor lungs, experts noted. Some experts anticipated the OCS Lung could alleviate the intensity and complexity of overall treatment after transplantation.

The OCS Lung would significantly increase health care costs for lung transplantation, experts concluded. However, experts anticipated the increased cost associated with purchase of the OCS

Lung would eventually be offset by increased revenue from preserving and transplanting more lungs and decreased costs from shorter lengths of stay and reduced complications.

Health disparities: Experts offered mixed comments on the impact of the OCS Lung on health disparities. Some experts thought health disparities would not be affected at all. Others concluded that the high costs associated with the OCS and lung transplantation and limited access to health care coverage in health disparate populations would further contribute to disparities in health.

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